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C07K 1/113, 19/00, A61P 43/00CURRIE, Richard [GB/GB]; 31 Seymour Street, Dundee  
DD2 1HA (GB). DOWNES, Peter [GB/GB]; 15 West  
Acres Drive, Wormit DD6 8NR (GB). CASAMAYOR,  
Antonio [ES/US]; Department of Molecular, Cellular and  
Developmental Biology, Yale University, New Haven, CT  
06520-8103 (US).

(21) International Application Number: PCT/GB00/01004

(74) Agent: MILES, John, S.: Eric Potter Clarkson, Park View  
House, 58 The Ropewalk, Nottingham NG1 5DD (GB).

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NL, PT, SE).(30) Priority Data:  
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— With international search report.

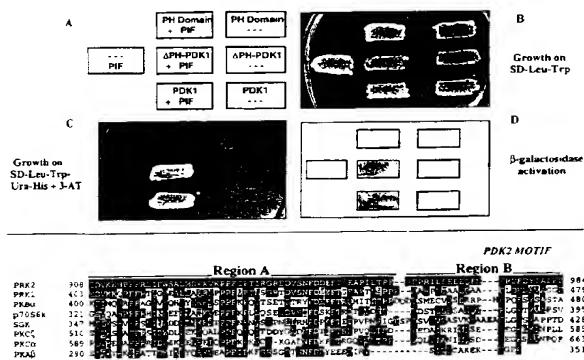
(71) Applicant (for all designated States except US): UNIVERSITY OF DUNDEE [GB/GB]; 11 Perth Road, Dundee  
DD1 4HN (GB).(88) Date of publication of the international search report:  
18 January 2001

(72) Inventors; and

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(75) Inventors/Applicants (for US only): ALESSI, Dario [GB/GB]; 309 Perth Road, Dundee DD2 1LG (GB). BALENDRAN, Anudharan [LK/GB]; Flat 26, Peterson Hall, 25 Roseangle, Dundee DD1 4LS (GB). DEAK, Maria [HU/GB]; 18 Forth Place, Dundee DD2 4HT (GB).

(54) Title: METHODS FOR ALTERING SUBSTRATE SPECIFICITY OF PHOSPHOINOSITIDE-DEPENDENT-PROTEIN KINASE 1 (PDK1)



(57) Abstract: A method of altering the substrate specificity of phosphoinositide-dependent protein kinase 1 (PDK1) wherein the said PDK1 is exposed to a polypeptide which comprises the amino acid sequence Phe/Tyr-Xaa-Xaa-Phe/Tyr-Zaa-Phe/Tyr wherein Zaa represents a negatively charged amino acid residue. The PDK1 with altered substrate specificity is capable of phosphorylating the underlined residue in a polypeptide with an amino acid sequence corresponding to the consensus sequence Phe/Tyr-Xaa-Xaa-Phe/Tyr-Ser/Thr-Phe/Tyr. The PDK1 with altered specificity may be useful in screening assays and for phosphorylating substrates having the above consensus sequence.

**WO 00/56864 A3**

## INTERNATIONAL SEARCH REPORT

Int'l Application No  
PCT/US 00/01004

A. CLASSIFICATION OF SUBJECT MATTER				
IPC 7	C12N9/12	C12Q1/48	C07K14/47	C12N15/63
	C12S3/14	C07K1/113	C07K19/00	C12N5/10
A61P43/00				

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C12Q C12S C07K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 41638 A (MEDICAL RES COUNCIL) 24 September 1998 (1998-09-24) cited in the application the whole document	16-21, 30,31
X	LE GOOD A.J. ET AL.: "Protein Kinase C Isotypes Controlled by Phosphoinositide 3-Kinase Through the Protein Kinase PDK1" SCIENCE, vol. 281, 25 September 1998 (1998-09-25), pages 2042-2045, XP002147843 cited in the application figure 2	15,17-21

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

19 September 2000

11/10/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patenttaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.  
Fax: (+31-70) 340-3016

Authorized officer

Schönwasser, D

## INTERNATIONAL SEARCH REPORT

Int'l Application No.  
PCT/00/01004

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PALMER R.H. ET AL.: "Expression, purification and characterization of the ubiquitous protein kinase C-related kinase 1." BIOCHEMICAL JOURNAL, vol. 309, no. 1, 1 July 1995 (1995-07-01), pages 315-320, XP000925935 page 316, column 1, paragraph 4 page 317, column 2, paragraph 3 -page 318, column 1, paragraph 1 ---	15,17-21
P,X	BALENDRAN A. ET AL.: "PDK1 acquires PDK2 activity in the presence of a synthetic peptide derived from the carboxyl terminus" CURRENT BIOLOGY, vol. 9, no. 8, 22 April 1999 (1999-04-22), pages 393-404, XP000925908 the whole document ---	1-6,12, 14-27, 30,32,33
P,X	VANHAESEBROECK B. ET AL.: "The PI3K-PDK1 connection: more than just a road to PKB" BIOCHEMICAL JOURNAL, vol. 346, no. 3, 15 March 2000 (2000-03-15), pages 561-576, XP000925911 page 565, column 2, line 14 -page 566, column 1, line 23 ---	1-6,12, 14-27, 30,32,33
P,X	BIONDI R.M. ET AL.: "Identification of a pocket in the PDK1 kinase domain that interacts with PIF and the C-terminal residues of PKA" THE EMBO JOURNAL, vol. 19, no. 5, 1 March 2000 (2000-03-01), pages 979-988, XP002147844 the whole document ---	1-6,12, 14-27, 30,32,33
T	US 6 001 622 A (HANNIGAN GREG ET AL) 14 December 1999 (1999-12-14) column 10, line 43 - line 54 ---	1-33
A	BELHAM C. ET AL.: "Intracellular signalling: PDK1--a kinase at the hub of things" CURRENT BIOLOGY, vol. 9, no. 3, 11 February 1999 (1999-02-11), pages R93-R96, XP000925940 the whole document -----	1-33

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 27-29 (incomplete)

Present claims 27 - 29 relate to compounds and the use of such compounds defined by reference to a desirable characteristic or property, namely to compounds identified as modulators of PDK1 activity in the presence of a polypeptide comprising the amino acid sequence

Phe/Tyr-Xaa-Xaa-Phe/Tyr-Zaa-Phe/Tyr (see claims 8-10), to compounds identified as being able to alter the substrate specificity of PDK1 (claims 11,12) and to compounds identified as being able to mimick the effect of a 3-phosphoinositide (claim 13).

The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds which are able to alter substrate specificity as claimed in claim 1 and disclosed on page 3, line 19 to page 4, line 9 and page 10, line 22 to page 13, line 2 of the description.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

**INTERNATIONAL SEARCH REPORT**

inform [REDACTED] on patent family members

Int [REDACTED] Application No

PCT/GB 00/01004

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9841638	A 24-09-1998	AU 6412498 A		12-10-1998
		EP 0983363 A		08-03-2000
US 6001622	A 14-12-1999	US 6013782 A		11-01-2000
		AU 717466 B		30-03-2000
		AU 7614696 A		17-07-1997
		CA 2239151 A		03-07-1997
		WO 9723625 A		03-07-1997
		EP 0870033 A		14-10-1998

## PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

MILES, John S.  
ERIC POTTER CLARKSON  
Park View House  
58 The Ropewalk  
Nottingham NG1 5DD  
GRANDE BRETAGNE

PCT

*JBN → SP*  
NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT

(PCT Rule 71.1)

*SAC*

Date of mailing (day/month/year)	20.06.2001
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Applicant's or agent's file reference  
DUNY/P22517PC

## IMPORTANT NOTIFICATION

International application No. PCT/GB00/01004	International filing date (day/month/year) 17/03/2000	Priority date (day/month/year) 19/03/1999
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Applicant

UNIVERSITY OF DUNDEE et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

## 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/I(B/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
Fax: +49 89 2399 - 4465

Authorized officer

Büchler, S

Tel. +49 89 2399-8090



# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference  DUNY/P22517PC	<b>FOR FURTHER ACTION</b>	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No.  PCT/GB00/01004	International filing date (day/month/year)  17/03/2000	Priority date (day/month/year)  19/03/1999
International Patent Classification (IPC) or national classification and IPC  C12N9/12		
Applicant  UNIVERSITY OF DUNDEE et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

- This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I    Basis of the report
- II    Priority
- III    Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV    Lack of unity of invention
- V    Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI    Certain documents cited
- VII    Certain defects in the international application
- VIII    Certain observations on the international application

Date of submission of the demand  18/10/2000	Date of completion of this report  20.06.2001
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer  Huber, A  Telephone No. +49 89 2399 8173



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB00/01004

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):  
**Description, pages:**

1-73                   as originally filed

**Claims, No.:**

1-33                   as originally filed

**Drawings, sheets:**

1/22-22/22           as originally filed

**Sequence listing part of the description, pages:**

1-9, filed with the letter of 12.05.00

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- the language of publication of the international application (under Rule 48.3(b)).
- the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- contained in the international application in written form.
- filed together with the international application in computer readable form.
- furnished subsequently to this Authority in written form.
- furnished subsequently to this Authority in computer readable form.
- The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB00/01004

the description,      pages:  
 the claims,      Nos.:  
 the drawings,      sheets:

5.  This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):  
*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**II. Priority**

1.  This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:  
 copy of the earlier application whose priority has been claimed.  
 translation of the earlier application whose priority has been claimed.

2.  This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:  
**see separate sheet**

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:  
 the entire international application.  
 claims Nos. 12, 27-29 (partially).

because:

the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB00/01004

- the claims, or said claims Nos. 12 (partially) are so inadequately supported by the description that no meaningful opinion could be formed.
- no international search report has been established for the said claims Nos. 27-29 (partially).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- the written form has not been furnished or does not comply with the standard.
- the computer readable form has not been furnished or does not comply with the standard.

**IV. Lack of unity of invention**

1. In response to the invitation to restrict or pay additional fees the applicant has:
  - restricted the claims.
  - paid additional fees.
  - paid additional fees under protest.
  - neither restricted nor paid additional fees.
2.  This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
  - complied with.
  - not complied with for the following reasons:  
**see separate sheet**
4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
  - all parts.
  - the parts relating to claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims 1, 4-13, 21-23, 27-33
	No: Claims 2, 3, 14-22, 24-26
Inventive step (IS)	Yes: Claims 1, 4-13, 21-23, 27-33

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB00/01004

No: Claims  
Industrial applicability (IA) Yes: Claims 1-33  
No: Claims

2. Citations and explanations  
**see separate sheet**

**VIII. Certain observations on the international application**

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

**Re Item II**

**Priority**

Since the priority date of present application appears to be validly claimed, documents cited as PX in the search report are disregarded.

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 27-29 have only been searched partially since they cover compounds for which there is no sufficient support in the application.

Consequently, also examination can be carried only for those parts of the claims which appear to be clear, supported and disclosed, i.e. those parts which relate to compounds which are able to alter substrate specificity as claimed in Claim 1 and disclosed on page 3, line 19 to page 4, , line 9 and page 10, line 22 to page 13, line 2 of the description.

In addition, also the method of Claim 12, relating to method of altering substrate specificity of PDK1 by exposing said PDK1 to a **compound identifiable** by the method of Claim 11, is considered to lack support. As for Claims 27-29, the disclosure provides support for the method of Claim 12 only for a limited number of compounds. Hence, examination of said claim is restricted to those compounds which are disclosed in the application.

**Re Item IV**

**Unity of invention**

The subject-matter of Claims 5-7 does not seem to be linked by a novel or inventive common concept with the subject-matter of the remaining claims. The subject-matter of Claims 1-4, 8-26 and 30-33 relates to PDK1 which has an altered substrate specificity such that it capable of phosphorylating protein kinase B at Ser473 in addition to Thr308 and to methods for obtaining PDK1 with said altered substrate specificity.

Claims 5-7 relate to a method of phosphorylating PRK2 by exposure to PDK1, to a

preparation comprising PDK1 and PRK2 and to method of identifying compounds that modulate the activation /phosphorylation of PRK2 by PDK1. Said claims do not require that the substrate specificity of PDK1 is altered. Thus, the only common feature which links Claims 5-7 to the remainder of the claims is the presence of PDK1 and its known phosphorylating activity. This common feature is, however, not novel, see e.g. D1.

Therefore, the application lacks unity of invention in the sense of Rule 13.1 PCT.

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Reference is made to the following documents:

- D1: WO 98 41638 A (MEDICAL RES COUNCIL) 24 September 1998 (1998-09-24) cited in the application
- D2: LE GOOD A.J. ET AL.: 'Protein Kinase C Isootypes Controlled by Phosphoinositide 3-Kinase Through the Protein Kinase PDK1' SCIENCE, vol. 281, 25 September 1998 (1998-09-25), pages 2042-2045, XP002147843 cited in the application
- D3: PALMER R.H. ET AL.: 'Expression, purification and characterization of the ubiquitous protein kinase C-related kinase 1.' BIOCHEMICAL JOURNAL, vol. 309, no. 1, 1 July 1995 (1995-07-01), pages 315-320, XP000925935
- D4: BELHAM C. ET AL.: 'Intracellular signalling: PDK1-a kinase at the hub of things' CURRENT BIOLOGY, vol. 9, no. 3, 11 February 1999 (1999-02-11), pages R93-R96, XP000925940

2. Novelty (Art. 33(2) PCT):

2.1 D1 discloses the recombinant production of PDK1. A PDK1 mutant lacking the C-terminal PH domain (aa 1-450) was expressed as GST-fusion protein in 293 cells (p. 73, l. 10-11). Another mutant consisting of residues 52-556 of PDK1 was also expressed in 293 cells (p. 70, l. 1-5).

Due to the unclear language "consisting essentially of residues 51-404" the

truncation mutants of D1 are considered to be embraced in the scope of Claim 16. The subject-matter of Claims 16-21 is therefore not new in view of D1.

2.2 The subject-matter of Claim 15 is not novel in view of D3. D3 discloses a synthetic C-terminal peptide of PRK1 comprising amino acid residues FLDFDF (page 315, right col., third paragraph). This peptide falls under the scope of Claim 15.

2.3 D2 discloses PKC $\zeta$  constructs comprising e.g. only the kinase domain (see Fig. 2A, construct f). The constructs were coexpressed with PDK1 in 293 cells and the expression products were immunoprecipitated. D2 therefore anticipates the subject-matter of Claims 15, 17-19, 22 and 24-26.

2.4 D2 further discloses cotransfection of myc-tagged PDK1 (aa 51-404) with full-length PKC $\zeta$  and immunoprecipitation of PDK1. Hence, D2 is also novelty-destroying for Claim 16 and the thereon dependent Claims 17-21.

2.5 Claim 2 relates to a preparation comprising PDK1 and an interacting polypeptide, wherein said preparation is substantially free of polypeptides with which PDK1 is naturally present or associated other than the interacting polypeptide or a substrate for PDK1. D2 discloses coexpression of PDK1 and PKC $\zeta$  in 293 cells. PDK1 and PKC $\zeta$  were immunoprecipitated as a complex. In its broadest sense, the preparation of Claim 2 encompasses said complex. Therefore, Claim 2 is considered to lack novelty over D2. Since PDK1 contacted with PKC $\zeta$  inherently must have altered substrate specificity, also the subject-matter of Claim 3 is anticipated by D2.

2.6 Claim 14 is formulated as a product-by-process. PDK1 known from the prior art, e.g. D1, cannot be distinguished from a protein kinase as defined in Claim 14. The functional feature that the protein kinase is capable of phosphorylating the Ser/Thr residue in the given consensus sequence of a polypeptide is an inherent feature of PDK1 which is achieved by exposing the protein to an interacting polypeptide. The claimed process of preparation does not alter the substrate specificity of PDK1 known from D1. Therefore, the protein of Claim 14 is not novel vis-à-vis the

protein of D1.

- 2.7 Claim 22 embraces any cell which contains a nucleic acid which can express PDK1 and a nucleic acid which can express a polypeptide having the indicated consensus sequence. The feature "recombinant nucleic acid" does not distinguish a cell which naturally expresses both PDK1 and e.g. PKC $\zeta$  or PRK1. The subject-matter of Claim 22 therefore lacks novelty over such naturally occurring cells.
3. Claims relating to methods of altering substrate specificity of PDK1 or of phosphorylating the Ser/Thr residue in the indicated consensus sequence are considered as being novel and also to involve an inventive step. The finding that the substrate specificity of PDK1 is altered by exposition of the protein with an interacting polypeptide is not derivable in an obvious manner from the prior art. On the contrary, it was assumed in the prior art (D1, D4) that a second, yet unidentified enzyme (termed provisionally PDK2) was responsible for phosphorylation of the said residue. Although the method of Claim 13 is in principal identical to the method described on page 27, l. 10-19 of D1, the method of D1 has not been applied to a PDK1 which has altered substrate specificity, i.e. to a PDK1 exposed to the interacting polypeptide.

**Re Item VIII**

**Certain observations on the international application**

1. The high number of independent claims results in a lack of clarity of the claims as a whole, since the plurality of independent claims makes it difficult, if not impossible, to determine the matter for which protection is sought, and places an undue burden on others seeking to establish the extent of the protection.  
The present set of claims therefore also lacks conciseness (Art. 6 PCT).
2. The term "consisting essentially of" in Claims 16 and 30 is unclear and leaves the reader in doubt as to the exact meaning of the technical features to which it refers thereby rendering the scope of the claims open to interpretation (Art 6 PCT).

# PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

To:  
 ERIC POTTER CLARKSON  
 Attn. Miles, John S.  
 Park View House  
 58 The Ropewalk  
 Nottingham NG1 5DD  
 UNITED KINGDOM

MW.

JW

sf

## PCT

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL SEARCH REPORT  
OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference <b>DUNY/P22517PC</b>	Date of mailing (day/month/year) <b>11/10/2000</b>
International application No. <b>PCT/GB 00/01004</b>	FOR FURTHER ACTION      See paragraphs 1 and 4 below  International filing date (day/month/year) <b>17/03/2000</b>
Applicant <b>UNIVERSITY OF DUNDEE et al.</b>	

1.  The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

**Where?** Directly to the International Bureau of WIPO  
 34, chemin des Colombettes  
 1211 Geneva 20, Switzerland  
 Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2.  The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3.  With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

Shortly after 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be selected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority   European Patent Office, P.B. 5818 Patenttaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer  <b>Peggy Frenzel</b>
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## NOTE TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

#### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

#### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

#### What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

## NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:  
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or  
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

### "Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

**It must be in the language in which the international application is to be published.**

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

### Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

### Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

## PATENT COOPERATION TREATY

## PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>DUNY/P22517PC</b>	<b>FOR FURTHER ACTION</b> see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. <b>PCT/GB 00/01004</b>	International filing date (day/month/year) <b>17/03/2000</b>	(Earliest) Priority Date (day/month/year) <b>19/03/1999</b>
Applicant <b>UNIVERSITY OF DUNDEE et al.</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of **5** sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).
- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search was carried out on the basis of the sequence listing:
  - contained in the international application in written form.
  - filed together with the international application in computer readable form.
  - furnished subsequently to this Authority in written form.
  - furnished subsequently to this Authority in computer readable form.
  - the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
  - the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2.  Certain claims were found unsearchable (See Box I).

3.  Unity of Invention is lacking (see Box II).

4. With regard to the title,

- the text is approved as submitted by the applicant.
- the text has been established by this Authority to read as follows:

**METHODS FOR ALTERING SUBSTRATE SPECIFICITY OF PHOSPHOINOSITIDE-DEPENDENT-PROTEIN KINASE 1 (PDK1)**

5. With regard to the abstract,

- the text is approved as submitted by the applicant.
- the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

- as suggested by the applicant.
- because the applicant failed to suggest a figure.
- because this figure better characterizes the invention.

**1**

None of the figures.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/01004

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7	C12N9/12	C12Q1/48	C07K14/47	C12N15/65	C12N5/10
	C12S3/14	C07K1/113	C07K19/00	A61P43/00	

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12N C12Q C12S C07K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 41638 A (MEDICAL RES COUNCIL) 24 September 1998 (1998-09-24) cited in the application the whole document ---	16-21, 30,31
X	LE GOOD A.J. ET AL.: "Protein Kinase C Isotypes Controlled by Phosphoinositide 3-Kinase Through the Protein Kinase PDK1" SCIENCE, vol. 281, 25 September 1998 (1998-09-25), pages 2042-2045, XP002147843 cited in the application figure 2 ---	15,17-21 -/-

 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

19 September 2000

Date of mailing of the international search report

11/10/2000

## Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patenttaan 2  
 NL - 2290 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.  
 Fax: (+31-70) 340-3016

## Authorized officer

Schönwasser, D

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/01004

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PALMER R.H. ET AL.: "Expression, purification and characterization of the ubiquitous protein kinase C-related kinase 1." BIOCHEMICAL JOURNAL, vol. 309, no. 1, 1 July 1995 (1995-07-01), pages 315-320, XP000925935 page 316, column 1, paragraph 4 page 317, column 2, paragraph 3 -page 318, column 1, paragraph 1	15, 17-21
P,X	BALENDRAN A. ET AL.: "PDK1 acquires PDK2 activity in the presence of a synthetic peptide derived from the carboxyl terminus" CURRENT BIOLOGY, vol. 9, no. 8, 22 April 1999 (1999-04-22), pages 393-404, XP000925908 the whole document	1-6, 12, 14-27, 30, 32, 33
P,X	VANHAESEBROECK B. ET AL.: "The PI3K-PDK1 connection: more than just a road to PKB" BIOCHEMICAL JOURNAL, vol. 346, no. 3, 15 March 2000 (2000-03-15), pages 561-576, XP000925911 page 565, column 2, line 14 -page 566, column 1, line 23	1-6, 12, 14-27, 30, 32, 33
P,X	BIONDI R.M. ET AL.: "Identification of a pocket in the PDK1 kinase domain that interacts with PIF and the C-terminal residues of PKA" THE EMBO JOURNAL, vol. 19, no. 5, 1 March 2000 (2000-03-01), pages 979-988, XP002147844 the whole document	1-6, 12, 14-27, 30, 32, 33
T	US 6 001 622 A (HANNIGAN GREG ET AL) 14 December 1999 (1999-12-14) column 10, line 43 - line 54	1-33
A	BELHAM C. ET AL.: "Intracellular signalling: PDK1--a kinase at the hub of things" CURRENT BIOLOGY, vol. 9, no. 3, 11 February 1999 (1999-02-11), pages R93-R96, XP000925940 the whole document	1-33

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 27-29 (incomplete)

Present claims 27 - 29 relate to compounds and the use of such compounds defined by reference to a desirable characteristic or property, namely to compounds identified as modulators of PDK1 activity in the presence of a polypeptide comprising the amino acid sequence Phe/Tyr-Xaa-Xaa-Phe/Tyr-Zaa-Phe/Tyr (see claims 8-10), to compounds identified as being able to alter the substrate specificity of PDK1 (claims 11,12) and to compounds identified as being able to mimick the effect of a 3-phosphoinositide (claim 13). The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds which are able to alter substrate specificity as claimed in claim 1 and disclosed on page 3, line 19 to page 4, line 9 and page 10, line 22 to page 13, line 2 of the description.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

**INTERNATIONAL SEARCH REPORT**International application No.  
PCT/GB 00/01004**Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.: 27-29 (incomplete)  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
  
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of Invention is lacking (Continuation of Item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
  
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
  
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/01004

Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 9841638	A	24-09-1998		AU 6412498 A EP 0983363 A		12-10-1998 08-03-2000
US 6001622	A	14-12-1999		US 6013782 A AU 717466 B AU 7614696 A CA 2239151 A WO 9723625 A EP 0870033 A		11-01-2000 30-03-2000 17-07-1997 03-07-1997 03-07-1997 14-10-1998